Extraintestinal Manifestations and Long-Term Complications of

Inflammatory Bowel Disease

The third in a series of educational newsletters
based on the proceedings of a roundtable held
December 12–13, 2001

PRESENTED BY:

The Office on Women's Health
of the
U.S. Department of Health and Human Services
and
The Society for Women's Health Research

SOCIETY FOR WOMEN'S HEALTH RESEARCH

IN COOPERATION WITH:

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This program is supported by an unrestricted educational grant from Procter & Gamble Pharmaceuticals, Inc.

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CLINICAL COURIER®

Vol. 20 No. 8 September 2002 ISSN 0264-6684

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EXTRAINTESTINAL MANIFESTATIONS AND LONG-TERM COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders of the gastrointestinal (GI) tract that may be accompanied by a number of potentially serious complications. Although the primary site of disease is the bowel, there are a multitude of extraintestinal manifestations that can arise in virtually any body system. These complications manifest themselves at different rates in men and women. Further, there are several long-term complications, including colorectal cancer and osteoporosis, which also can add to the overall burden of these diseases. In December 2001, leading experts and representatives from key organizations met to review the state of the art in the management of inflammatory bowel disease (IBD). This newsletter highlights those aspects of IBD that accompany and complicate this disorder. Clinical knowledge of the full spectrum of possible complications is necessary so that all facets of disease can be effectively managed.

EXTRAINTESTINAL MANIFESTATIONS OF IBD

UC and CD are associated with numerous chronic inflammatory disorders in organ systems distant from the gut. These extraintestinal manifestations can be quite common (in approximately 25% of patients), complicate the management of IBD, and may be a significant source of morbidity and mortality.[1,2] More than 100 have been described, and they can involve almost any organ or organ system, including musculoskeletal, skin and mucous membranes, ocular, hepatobiliary, bronchopulmonary, cardiac, hematologic, renal and genitourinary, pancreatic, endocrine and metabolic, and neurologic.[3] The most common extraintestinal manifestations occur in the skin, eyes, joints, and biliary tract (Table 1).[3] Extraintestinal manifestations can occur at any time during the course of IBD. Although some may precede IBD, most occur concomitantly with it and are influenced by clinical disease activity.[2] Therefore, many extraintestinal manifestations are controlled as the primary disease, IBD, is contained through effective treatment.

TABLE 1
COMMON EXTRAINTESTINAL MANIFESTATIONS OF IBD

Dermatologic	
• Erythema nodosum	• Psoriasis
• Pyoderma gangrenosum	• Epidermolysis bullosa acquisita
• Sweet's syndrome	• Perianal skin tags
• Metastatic Crohn's disease	• Polyarteritis nodosa
Ocular	
• Conjunctivitis	• Chorioretinitis with retinal detachment
• Uveitis/iritis	• Crohn's keratopathy
• Episcleritis	• Posterior segment abnormalities
• Scleritis	• Retinal vascular disease
• Retrobulbar neuritis	
Musculoskeletal	
• Peripheral arthritis (colitic arthritis)	• Clubbing and hypertrophic osteoarthropathy
• Granulomatous monoarthritis	• Periosteitis
• Granulomatous synovitis	• Osteoporosis/osteomalacia
• Rheumatoid arthritis	• Rhabdomyolysis
• Sacroiliitis	• Pelvic osteomyelitis
• Ankylosing spondylitis	
• Relapsing polychondritis	
Hepatobiliary	
• Primary sclerosing cholangitis (PSC)	• Fatty infiltration of the liver
• Small duct PSC (pericholangitis)	• Cholelithiasis/gallstones
• Carcinoma of the bile ducts	• Autoimmune hepatitis

Adapted with permission from Levine JB. In: Kirsner JB, ed. *Inflammatory Bowel Disease.* 5th ed. Philadelphia, Pa: WB Saunders; 2000:397-409.

LEARNING OBJECTIVES

After completing this program, participants will be able to discuss and summarize current findings regarding the complications of inflammatory bowel disease (IBD) and identify knowledge gaps as they apply to:

- The spectrum of extraintestinal manifestations of IBD
- The risk of colorectal cancer (CRC) and other malignancies in patients with IBD
- Use of medical therapy for CRC prevention
- Endoscopic surveillance of dysplasia and clinical decision-making regarding biopsy findings
- The factors underlying osteoporosis in patients with IBD
- Strategies for screening, prevention, and treatment of osteoporosis

Target audience: US and Canadian gastroenterologists and fellows

Pathophysiologic Links Between IBD and Extraintestinal Manifestations

There are many intriguing, unanswered questions regarding extraintestinal manifestations. Among the primary questions to be resolved are: What are the common genetic and pathogenic links between IBD and extraintestinal manifestations? Is colitis an "intestinal manifestation" of systemic immune dysfunction? Does aggressive use of first-line treatment or immunomodulators change the natural course of the disease? Does response (or lack of response) to treatment provide clues to the pathogenesis of extraintestinal manifestations? Does aggressive management of colitis, or use of immunomodulators, change the natural history of extraintestinal manifestations? Does response to biologic agents offer clues to the interaction between the gut and various organ systems?

Although the underlying pathophysiologic factors are not well understood, it seems clear that the most common extraintestinal manifestations all are immunologically mediated. It is theorized that they are extraintestinal responses to events that originate in the intestine. The cells and cytokines that are generated during the dysregulated inflammatory response in the gut are believed to enter the systemic circulation and traffic to distant sites within the body, where they stimulate a chronic inflammatory state.[3] Why the specific extraintestinal organs are targeted is unknown. However, the

fact that immunosuppressive treatments are effective for many of these extraintestinal manifestations provides evidence that immune dysregulation is a shared feature of IBD and its extracolonic complications.[2]

Evidence that genetic factors play a role is provided by the finding that major histocompatibility antigen genes are associated with particular extraintestinal manifestations, including uveitis/iritis, ankylosing spondylitis, and primary sclerosing cholangitis (PSC). Major histocompatibility genes influence host immune responses to specific antigens; associations between certain haplotypes and extraintestinal manifestations suggest that they somehow contribute to the dysregulated immune responses that underlie extraintestinal manifestations.[3] The human leukocyte antigen (HLA)-B27 haplotype is associated with both uveitis/iritis and ankylosing spondylitis.[4] The HLA-B8, DR3, and DRw52 haplotypes are associated with PSC.[5,6]

Epidemiology

Greenstein and colleagues, in a classic study of 700 patients with UC or CD, were among the first to provide information on the epidemiology of extraintestinal manifestations.[7] Joint manifestations included arthritis in 23% of patients and ankylosing spondylitis in 4%. Cutaneous manifestations occurred in approximately 15% of all patients; the most common were erythema nodosum (in approximately 6%) and pyoderma gangrenosum (in approximately 2%). Four percent of patients had eye disease, including conjunctivitis, recurrent episcleritis, and uveitis. An additional 4% were observed to have mouth lesions.[7] Although Greenstein, *et al.* identified additional, less frequent extraintestinal manifestations, they considered the manifestations in the joints, skin, eyes, and mouth to be distinguished by their close correlation with underlying disease activity, shared immunologic etiology, and responsiveness to medical or surgical treatment of IBD. Importantly, they noted that multiple manifestations occurred in a third of patients.[7]

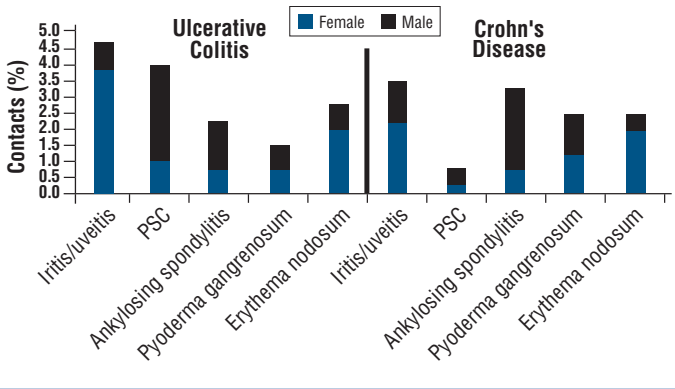
The most recent epidemiologic information comes from a population-based study that reported the prevalence of extraintestinal manifestations and their relationship to disease diagnosis and gender. Bernstein and colleagues assessed the presence of PSC, ankylosing spondylitis, iritis/uveitis, pyoderma gangrenosum, and erythema nodosum among 4,454 subjects with a known diagnosis of IBD for at least 10 years.[8] Arthritis was not assessed. The 10-year period prevalence rates based on five or more health system contacts for UC and CD in relation to gender are shown in Figure 1.[8] In contrast to other studies, a smaller fraction of patients were found to have extraintestinal manifestations, although this finding may be explained by the fact that the arthritis prevalence was not assessed. A total of 6.2% of patients with IBD had one of the five major extraintestinal manifestations studied in this report, but only 0.3% of patients had multiple extraintestinal manifestations. Iritis/uveitis was the most common extraintestinal manifestation, in 2.2% of women and 1.1% of men. Iritis/uveitis was more common among women, particularly those with UC (3.8%). PSC was most common among men with UC (3%). Ankylosing spondylitis was more common among men, particularly those with CD (2.7%). Pyoderma gangrenosum was more common in CD, equally so among men and women (1.2%). Erythema nodosum was present in equal proportion in UC and CD, but was more common among women (1.9%).[8] The basis for gender-related differences is not known. Wagtmans and colleagues, in their study of patients with CD, also found that arthritis, erythema nodosum, and ocular manifestations occurred more often in women than in men.[9]

Descriptions and Definitions of Common Extraintestinal Manifestations

Dermatologic Extraintestinal Manifestations

The most predominant cutaneous disorders are erythema nodosum and pyoderma fixorphan gangrenosum. Other skin manifestations are listed in Table 1 (Page 1).

FIGURE 1
TEN-YEAR PERIOD PREVALENCE RATES OF EXTRAINTESTINAL MANIFESTATIONS IN ULCERATIVE COLITIS AND CROHN'S DISEASE, BY GENDER



PSC=primary sclerosing cholangitis.
Bernstein CN, *et al. Am J Gastroenterol.* 2001;96:1116-1122.

Extraintestinal Manifestations and Long-Term Complications of Inflammatory Bowel Disease, as published in this *Clinical Courier*®, is the third in a series of newsletters based, in part, on the proceedings of a roundtable that was held on December 12-13, 2001, in Washington, D.C. Learning objectives of that roundtable were as follows:

By the end of the program, participants were able to discuss what is known about sex differences and were able to summarize current findings and identify knowledge gaps as they apply to the:

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with inflammatory bowel disease (IBD)
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Psychosocial challenges IBD patients face
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

Statement of Need: Strategies for the management of IBD are continuing to evolve as the result of research advances, growing clinical experience, and an expanding therapeutic armamentarium. However, the management of various complications and extraintestinal manifestations of IBD remains a challenge for physicians treating the underlying disease. These complications have serious implications for the long-term welfare of patients with IBD and can even be elicited by the very medications used to treat the conditions. As many as 25% of all patients with IBD will experience extraintestinal manifestations of their disease at some point, not including such insidious morbidities as osteoporosis and colorectal cancer.[1] An appreciation of these significant extraintestinal manifestations of IBD is critical to developing appropriate therapeutic regimens that can positively impact the spectrum of disease presentation and its systemic effects on the patient. Awareness of these issues will help physicians become better equipped to meet the challenges of IBD in daily clinical practice and will support the practice of evidence-based medicine.

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olsalazine sodium	Dipentum®		
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Glucocorticoids (hydrocortisone, prednisone, and prednisolone)	Various	Ulcerative colitis and numerous other indications	N/A
Hormone replacement therapy	Various	Symptoms associated with menopause, vulvar/vaginal atrophy, and prevention of osteoporosis	N/A
Infliximab (anti-TNF-α monoclonal antibody)	Remicade®	Moderately to severely active Crohn's disease refractory to conventional treatments, fistulizing Crohn's disease, and rheumatoid arthritis	Ulcerative colitis and other inflammatory disorders
Methotexate	Various	Neoplastic disease, psoriasis, and rheumatoid arthritis	Crohn's disease, ankylosing spondylitis, primary sclerosing cholangitis
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	Protopic®	Atopic dermatitis	
Thalidomide	Thalomid™	Erythema nodosum leprosum	Ankylosing spondylitis
Ursodiol (ursodeoxycholic acid)	Urso®, Actigall®	Primary biliary sclerosis, gallstones	Primary sclerosing colangitis

TNF=tumor necrosis factor; N/A= not available.

Erythema nodosum is an immunologically mediated disorder characterized by a lymphocytic and histiocytic infiltrate.[10] It characteristically presents as one or more hot, red, exquisitely tender, symmetrically distributed subcutaneous nodules. They are generally found on the extensor surfaces of the lower legs, but they also may occur on the ankles, calves, thighs, and arms. The diameter of nodules ranges from 1 to 10 cm. New nodules may appear as older nodules fade with a bruiselike appearance. Ulceration is rare, and complete healing occurs within a month or so after nodules appear. Erythema nodosum is a marker for a number of systemic diseases, including tuberculosis, sarcoidosis, and IBD. When it is associated with IBD, it typically occurs at times of clinically active disease and follows the same course.[3,10]

Pyoderma gangrenosum is an ulcerative cutaneous condition that was first described in 1930.[11] It is associated with IBD, arthritides, and hematologic conditions. Among all patients with pyoderma gangrenosum, 15% to 20% have IBD.[12] It classically has been associated with UC, with an incidence of 1% to 5%, but is also found in association with CD.[1] Pyoderma gangrenosum lesions develop rapidly, beginning as small erythematous violaceous papules that spread concentrically. They quickly evolve into tender pustules, and the central portion of the lesion undergoes necrosis and ulceration. Lesions are found on the neck, the trunk, and, above all, anterior tibial surfaces of the lower legs.[13] When associated with IBD, pyoderma gangrenosum typically occurs when disease is active. Symptoms sometimes occur before the diagnosis of IBD is made.[1] Topical or local medical therapies include compresses, antibacterial agents, corticosteroids, and immunosuppressants. Systemic therapy includes corticosteroids, sulfones, antibiotics, and other immunosuppressive agents.[12] In UC or CD, treating the underlying disease provides the opportunity to also affect the skin disease.

Ocular Extraintestinal Manifestations

Numerous ocular extraintestinal manifestations are associated with IBD (Table 1, Page 1). Episcleritis is usually associated with active bowel disease and often manifests with other extraintestinal manifestations, particularly those of the joints.[2] In contrast, uveitis/iritis is a potentially serious complication associated with HLC-TS27 and follows an independent course from IBD. It manifests as a painful eye with blurring, photophobia, headache, iridospasm, and abnormal papillary response. Systemic or topical corticosteroids usually are effective in treatment, but patients with refractory cases may require immunosuppressive treatment.[3]

Musculoskeletal Extraintestinal Manifestations

Patients with IBD have two major forms of joint involvement, a peripheral (colitic) arthritis and an axial form that includes ankylosing spondylitis or sacroiliitis.[14] Peripheral arthritis affects approximately 15% to 20% of patients with IBD. It is migratory, nondeforming, and commonly asymmetric. It typically affects the large joints of the lower extremities.[2] Its course follows that of IBD, with flares occurring during active bowel disease.[8] The incidence of peripheral arthritis is higher in CD than in UC.[3] Treatment is directed primarily against the underlying IBD. If this does not control the arthritis, then further therapies such as intraarticular corticosteroid injections may be employed.[14]

Ankylosing spondylitis affects a much smaller percentage of patients with IBD, occurring in about 3% to 6%.[2] Males are more affected than females. Unlike peripheral arthropathy, it can precede bowel symptoms and follows an independent course. Ankylosing spondylitis can be progressive and result in permanent skeletal damage, but this is unusual in IBD patients.[3] A number of anti-inflammatory and immunomodulatory agents have been used in ankylosing spondylitis, including sulfasalazine, corticosteroids, methotrexate, and thalidomide. A recent open-label pilot study assessed the effects of infliximab in 21 treatment-resistant patients with various subtypes of spondyloarthropathy.[15] Patients with active disease received three infusions of 5 mg/kg infliximab at weeks 0, 2, and 6. Infliximab treatment was associated with a fast and significant improvement of axial and peripheral articular manifestations ($P \leq .01$ for all criteria assessed).[15] However, a recent study on the safety of anti–tumor necrosis factor-α (anti-TNF-α) therapies in inflammatory arthritides has shown that such therapies may be associated with neurologic adverse events suggestive of demyelination.[16] The authors of this study propose that further surveillance and studies are needed to better define the safety of anti-TNF-α therapy.[16] Infliximab is also not appropriate for patients with concomitant congestive heart failure[17] and may reactivate latent tuberculosis.[18,19]

Hepatobiliary Extraintestinal Manifestations

Hepatobiliary complications are among the most common and potentially serious complications associated with IBD (Table 1, Page 1). PSC, the primary type of hepatic complication, is characterized by inflammation, obliteration, and fibrosis of both intrahepatic and extrahepatic bile ducts, which eventually leads to biliary cirrhosis.[20] It is mainly associated with CD.[8] Although it used to be regarded as a rare medical curiosity, the advent of endoscopic retrograde cholangiography has resulted in its increased recognition. After chronic hepatitis C and alcoholic cirrhosis, it is one of the most common indications for liver transplantation.[20] Unfortunately, there is no effective medical therapy for PSC. Its medical management is aimed at symptoms and complications, and therapy of the underlying disease process. Liver transplantation is the only effective treatment.[20] A variety of immunomodulatory, anti-inflammatory, and antifibrotic agents have been used in PSC to little effect. These include corticosteroids, azathioprine (AZA), D-penicillamine, colchicine, cyclosporine, ursodeoxycholic acid, methotrexate, pentoxifylline, and tacrolimus.[20] Although therapy with ursodeoxycholic acid results in reduced elevations in liver enzymes, this treatment has not yet been proven to delay the development of biliary tract strictures or the evolution to biliary cirrhosis.

Other Extraintestinal Manifestations

Oral lesions are a common manifestation in IBD. Aphthous stomatitis is reported to occur in 5% of patients with UC and 20% of patients with CD.[14] These lesions typically follow the course of IBD and, therefore, encourage optimal maintenance strategies for their prevention. Other, rarer extraintestinal manifestations include renal complications, such as renal stones and amyloidosis, and hematologic extraintestinal manifestations, including anemia and hypercoagulation abnormalities.[3]

Extraintestinal manifestations associated with IBD encompass a vast, heterogeneous group of diseases. In most cases, treatment of underlying bowel disease will control the extracolonic manifestation. Their relative rarity, however, precludes controlled trials of medical therapies. Although this is so, investigators in the field of IBD are encouraged to report the response of extraintestinal manifestations to tested medications in order to further the goal of finding effective treatment. In addition, scientific and clinical research in these diseases should incorporate the expertise of many disciplines, including rheumatology, ophthalmology, dermatology, and gastroenterology.

COMPLICATIONS OF IBD: CANCER

The first case of cancer in a patient with IBD was reported in 1925.[21,22] Since then, accumulated evidence from case reports, case series, and population-based studies has confirmed this risk. Patients with UC have an increased risk of colorectal cancer (CRC) that increases with duration of disease, age, and extent of disease.[23]

TABLE 2
INCREASED RISKS FOR CANCER AMONG PATIENTS WITH IBD COMPARED TO MATCHED NON-IBD COHORTS

	Ulcerative Colitis	Crohn's Disease	Total IBD
Cancer Site	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
Colon	2.75 (1.91-3.97)	2.64 (1.69-4.12)	2.71 (2.04-3.59)
Rectum	1.90 (1.05-3.43)	1.08 (0.43-2.70)	1.56 (0.95-2.57)
Small intestine	Undefined	17.40 (4.16-72.9)	10.40 (3.02-36.1)
Liver and biliary tract	3.96 (1.05-14.9)	5.22 (0.96-28.5)	4.38 (1.54-12.4)
Lymphoma	1.03 (0.47-2.24)	2.40 (1.17-4.97)	1.52 (0.90-2.57)

IRR=incidence rate ratio; CI=confidence interval.
Bernstein CN, *et al. Cancer.* 2001;91:854-862.

Recent evidence suggests that this risk also is increased when there is a concurrent cancer (CRC) that increases with duration of disease, age, and extent of disease.[23] Recent evidence suggests that this risk also is increased when there is a concurrent diagnosis of PSC.[24] Patients with CD have an increased risk of colon cancer, which is associated with an early diagnosis (before 30 years of age) and greater extent of disease.[25,26] In addition, there have been several reports of an increased risk for extraintestinal cancers. Subsequent sections of this newsletter contain reviews of evidence for the increased cancer risk in patients with IBD, treatments that decrease the risk of CRC, and strategies for dysplasia surveillance.

Incidence of Cancer in IBD

Colorectal Cancer

Population-based studies have confirmed the increased incidence of cancer that was first described in case reports and case series reviews. The most recent study, by Bernstein and colleagues, has provided new data on and additional insights into these risks.[27] It used an IBD database linked to a comprehensive cancer registry to determine the incidence rates of various types of cancer over a 14-year period. The incidence among a North American population of patients with IBD was compared to a non-IBD population that was matched for age, gender, and geographic location.[27] An increased incidence rate ratio (IRR) of colon cancer for both UC and CD patients was observed. This increased risk was greater among subjects less than 40 years of age and was more prominent in men than women. Patients with UC (but not CD) had an increased IRR of rectal cancer. Conversely, patients with CD (but not UC) had an increased risk of small-intestine cancer (Table 2).[27] These data corroborate and strengthen previous evidence for the risk of CRC in patients with IBD.[23,25,26,28,29]

Extraintestinal Malignancies

There have been numerous case reports suggesting that IBD is associated with an increased risk of hematologic malignancies. An increased incidence of leukemia has been noted among patients with UC, and an increased incidence of lymphoma has been reported for patients with UC or CD.[30,31] Although population-based studies from Denmark and Sweden have not confirmed these findings,[28,29,32] Bernstein and colleagues demonstrated an increased risk of hematologic cancer in their study (Table 2).[27] The incidence of lymphoma was increased in male patients with CD (IRR = 3.63; 95% CI, 1.53-8.62). These findings are of particular concern given that immunomodulatory therapies may themselves contribute to an increased risk of hematologic cancer in immunocompromised patients.[27,33] A chart review of all patients with hematologic malignancies in the Bernstein study revealed that no immunomodulatory therapy other than corticosteroids had been used. Nevertheless, this potential for an increased risk of lymphoma in male patients with CD, even in the absence of immunomodulating therapy, must be borne in mind when such therapies are considered.[27]

An increased incidence of hepatobiliary cancers has been demonstrated among patients with UC in several population-based studies.[28,29] Bernstein and colleagues have confirmed this risk in patients with UC and also demonstrated an increased risk for hepatobiliary cancer in patients with CD (Table 2).[27]

Some studies have found a substantially higher risk of other types of malignancies in patients with IBD. For example, a population-based study from Sweden demonstrated a higher incidence of squamous cell skin cancer in patients with CD and higher rates of connective tissue and brain cancer among patients with UC.[32] Bernstein and colleagues did not show any statistically significant associations between UC or CD and any other type of extraintestinal malignancies other than lymphoma and hepatobiliary cancer, as previously noted.[27]

CRC Prevention

Two studies provide evidence that long-term therapy with 5-aminosalicylates (5-ASAs) may confer protection against CRC. One study assessed the impact of long-term sulfasalazine therapy on the natural course of UC.[34] Patients who were adherent to long-term treatment were significantly less likely to develop CRC than those who were nonadherent (3% vs. 31%, respectively; $P<.001$). A second study sought to identify risk factors for CRC—in addition to increased duration and extent of disease and increasing age—among patients with UC.[35] 5-ASA therapy substantially reduced the risk of CRC. The protective effect was greatest with mesalamine, which reduced CRC risk by 81%. Although protection was independent of dose, it was significant at mesalamine dosages of at least 1.2 g/day ($P<.00001$). Sulfasalazine also conferred protection, although the effect was less pronounced and seen only at dosages greater than 2 g/day (equivalent to >800 mg/day mesalamine).[34] A greater protective benefit of even higher doses of mesalamine is not known, but may be encouraged since the agent does not produce dose-related side effects.[35,36] The variables that most influenced CRC risk are provided in Table 3.[35]

TABLE 3
ADJUSTED ODDS RATIOS FOR MOST INFLUENTIAL VARIABLES FOR CRC RISK

Variable	Odds Ratio	95% CI	*P*-Value
No drug treatment	—	—	—
Mesalamine			
<1.2 g/day	0.18	0.02-1.92	.16
≥1.2 g/day	0.19	0.06-0.61	.006
Sulfasalazine			
<2 g/day	0.93	0.22-3.91	.92
≥2 g/day	0.85	0.32-2.26	.75
Other (olsalazine, balsalazide)			
Variable doses	1.21	0.08-18.97	.89
Contact with doctor			
0	—	—	—
1 to 2 per year over the course of disease	0.42	0.15-1.18	.10
>2 per year over the course of disease	0.16	0.04-0.60	.007
CRC in any relative			
No	—	—	—
Yes	6.84	0.80-58.60	.08
Colonoscopies after diagnosis			
0	—	—	—
1 to 2 over the course of disease	0.33	0.11-1.01	.05
>2 over the course of disease	0.55	0.18-1.71	.30

CRC=colorectal cancer.
Adapted with permission from Eaden J, *et al. Aliment Pharmacol Ther.* 2000;14:145-153.

Connell and colleagues have assessed the impact of AZA treatment on the risk of cancer in 755 patients with IBD.[37] Among patients with extensive chronic UC, there was no difference in cancer frequency between the patients who had received AZA and those who had not.

Dysplasia Surveillance

The increased risk of CRC in patients with IBD has led physicians to use endoscopic surveillance as a potential means of identifying precancerous lesions or cancers at an early, curable stage. Dysplasia is defined as a neoplastic change in colonic mucosa without invasion into the lamina propria.[38] It can be a harbinger of cancer development or an indication that cancer is already present. Endoscopic surveillance with biopsies searching for dysplasia, however, is quite controversial.[39] It is endorsed as the standard of care in patients with UC, and a recent study in selected patients with CD suggests it should be strongly considered in patients with chronic extensive Crohn's colitis.[40] Even so, a randomized controlled study proving the benefit of dysplasia-surveillance colonoscopy has not been performed.[41] Further, there is no

standard approach to the process of screening, there are several important limitations to its use, and many physicians do not understand the meaning of dysplasia or the implications of its various grades.[42]

Despite these caveats, endoscopic dysplasia surveillance represents the best available tool at the present time. A rational approach to screening is provided by Bernstein.[39] Dysplasia surveillance should be initiated at eight years of disease, and as many biopsies as possible should be obtained. At least eight sites should be biopsied with at least four biopsies per site. An increased number should be obtained from the sigmoid colon and rectum, because these sites have a higher incidence (>50% of observed instances) of CRC in UC.[43,44] A second opinion should be sought if the findings are indefinite or low-grade or high-grade dysplasia.[39] If the results are indefinite, a repeat endoscopy should be performed within 3 to 6 months, with more intensive treatment if there is active inflammation. In patients with UC, a finding of definite dysplasia, regardless of grade, or a dysplasia-associated lesion or mass frequently is associated with the presence of cancer and should be a strong indication for colectomy.[39]

In contrast, if the initial endoscopy findings are negative at eight years of disease, surveillance should be performed every 1 to 3 years until disease duration reaches 20 years. After this point, the frequency of surveillance should be increased to once every year. Because the risk of cancer rises with increased duration of disease, some clinicians, but certainly not all, suggest considerations for prophylactic colectomy.[39] Patients with UC should be made aware of the risk of CRC development so that they can address changes in their usual pattern of disease early and so that they can participate in decisions regarding surveillance issues. As previously noted, a recent study suggests that dysplasia surveillance should be strongly considered in patients with chronic extensive Crohn's colitis.[40]

Given the high cost of surveillance in patients with long-term disease, as well as the finding that dysplasia may indicate cancer already is present, several researchers have attempted to better refine this practice. Rubin and colleagues have reported that abnormal epithelial DNA content (aneuploidy) in biopsy specimens from patients with UC correlates with and predicts histologic progression to dysplasia.[45] They estimated that a minimum of 18 biopsies would be required to have a 95% sensitivity of finding any grade of neoplasia. They suggest that more intensive and frequent colonoscopic surveillance should be reserved for the small minority of patients with aneuploidy, whereas patients without aneuploidy may require less frequent surveillance.[45] However, at the present time, flow cytometric analyses of biopsies and measurement of p53 antigen staining remain investigational techniques.

COMPLICATIONS OF IBD: OSTEOPOROSIS

Osteoporosis and its sequelae—fractures of the hip, spine, wrist, and other skeletal sites—are a significant public health problem in the United States. In contrast to many other clinical areas, osteoporosis has been most studied in female patients, particularly postmenopausal women. Large and continuing research efforts have defined the scope of the problem in this population and identified specific agents for its prevention and treatment. Osteoporosis is the underlying factor in an estimated 1.5 million fractures each year.[46] In women, the most rapid bone loss occurs in the first year following cessation of menstruation. Consequently, Chrischilles and colleagues have estimated that more than half of all 50-year-old women will sustain an osteoporosis-related fracture during their lifetime.[47] The morbidity and mortality associated with osteoporotic fractures are substantial, and hip fractures have particularly dire consequences: the mortality rate can reach 10% to 20% in the 6 months following fracture.[46] Half of patients with hip fracture will not be able to walk without assistance, and 25% will require long-term care.[46] In addition, medical treatment for osteoporotic fractures confers a substantial economic burden. In 1995, it was estimated that health-care expenditures for osteoporosis in the United States reached $13.8 billion.[48]

Although attention has largely focused on postmenopausal women as well as elderly persons of both sexes, osteoporosis is a common clinical problem in IBD. In fact, the prevalence of osteoporosis in patients with IBD is reported to be approximately 20% to 30%.[49] This necessitates that physicians who treat patients with IBD be aware of the risks, since preventive approaches often are effective in ameliorating this condition. It is essential, in particular, that physicians know that all their female patients are at risk as they approach menopause. Not only does their sex itself represent a special concern, but the additional IBD-related risks for osteoporosis mandates that this population be managed with extreme care.

Factors in IBD-Related Osteoporosis

Patients with IBD face both general risk factors for osteoporosis as well as ones specifically related to IBD (Table 4).[50,51] Osteoporosis may be caused by drugs that are used to treat IBD, including corticosteroids, cyclosporine, and methotrexate. Inflammatory cytokines themselves can affect bone-remodeling processes that result in increased bone resorption. Patients with IBD may become malnourished or malabsorb certain nutrients, specifically vitamin D and calcium. The estimated prevalence of vitamin D deficiency has been shown to be 30% or higher in patients with CD and has been reported to be as high as 62% in patients with CD who have undergone small bowel resection.[50] Another factor is hypogonadism, which is reported to occur more frequently in women than in men (25% of female patients vs 10% of male patients with IBD).[52]

Corticosteroid-Induced Bone Loss

An unfortunate side effect of corticosteroid therapy is drug-related osteoporosis. Corticosteroids induce this effect through increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation. Bone loss occurs on initiation of corticosteroid therapy, most rapidly in the first 6 months of drug use. Skeletal effects are both dose and duration dependent.[53] van Staa and colleagues reported that daily prednisone doses of 7.5 mg and greater often result in substantial bone loss and increased fracture risk.[54] The rate of hip fracture increased by 77% in patients whose daily oral dose was 2.5 to 7.5 mg and 127% in those on daily doses of 7.5 mg or higher. Further, fracture rates in women were shown to increase exponentially with age, with particular progression among women who used high doses of corticosteroids.[54]

The prevalence of vertebral fracture risk in relation to age, bone density, and corticosteroid use was assessed by Naganathan and colleagues among 229 corticosteroid-

TABLE 4
GENERAL AND IBD-SPECIFIC RISK FACTORS FOR OSTEOPOROTIC FRACTURE

General Risk Factors

- Personal history of fracture as an adult
- History of fracture in first-degree relative
- Caucasian or Asian race
- Advanced age
- Female sex
- Dementia
- Poor health/frailty
- Current cigarette smoking
- Low body weight (<127 lb)
- Estrogen deficiency
  - Early menopause (<45 years of age) or bilateral ovariectomy
  - Prolonged premenopausal amenorrhea (>1 year)
- Low calcium intake (lifelong)
- Alcoholism
- Impaired eyesight despite adequate correction
- Recurrent falls
- Inadequate physical activity
- Nulliparity

IBD-Related Risk Factors

- Drugs (cyclosporine, methotrexate, corticosteroids)
- Inflammatory cytokines (IL-6, IL-1, TNF-α)
- Vitamin D deficiency
- Calcium malabsorption
- Hypogonadism
- Hyperalimentation

IL=interleukin; TNF=tumor necrosis factor.

Valentine JF, Sninsky CA. *Am J Gastroenterol.* 1999;94:878-883. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Available at: http://www.nof.org/_vti_bin/shtml.dll/physguide/index.htm.

treated patients (158 females, 71 males) and 286 controls.[55] In comparison to healthy controls, corticosteroid-treated patients 60 years of age or older had an increased prevalence of vertebral deformities that increased with each decade of age (Figure 2). In addition, the mean bone mineral density (BMD) Z scores of the spine and femur were lower in corticosteroid-using patients than in control subjects. It is clear that the combination of corticosteroid use and increasing age places patients at an increased risk for lowered BMD and vertebral fracture.

Budesonide is a newer oral corticosteroid that has been approved recently by the Food and Drug Administration for inducing remission in patients with mild to moderate CD involving the ileocecal area. Its use in patients with active CD has been associated with fewer short-term corticosteroid-related adverse effects,[56] but it is ineffective as maintenance therapy.[57] It is important to note that budesonide's long-term safety profile has yet to be established, and, as such, clinicians should approach its use and potential impact on bone loss as they would the other agents in this class.

The American College of Rheumatology Task Force on Osteoporosis Guidelines has published recommendations for the prevention and treatment of corticosteroid-induced osteoporosis.[53] These may be useful to adopt for patients with IBD, as guidelines for the prevention and treatment of osteoporosis in patients with IBD are currently being developed. Patients should be given the lowest effective dose of glucocorticoid possible, and lifestyle modifications such as smoking cessation, decreased alcohol consumption, and weight-bearing exercise should be encouraged.[53] All patients should begin osteoporosis prophylaxis at the initiation of corticosteroid therapy. Because a substantial proportion of patients with IBD, particularly CD, have osteoporosis at the time of diagnosis, prior to introduction of corticosteroids, a BMD measurement should be obtained, both to determine the patient's risk for osteoporosis independent of treatment and to provide a baseline measurement for monitoring changes in bone mass.[53] Calcium and vitamin D supplementation should begin, as well as pharmacologic therapy to prevent bone loss, if the results of the BMD measurement indicate low values.[53] Unless contraindicated, hormone replacement therapy (HRT) should be initiated in postmenopausal women.

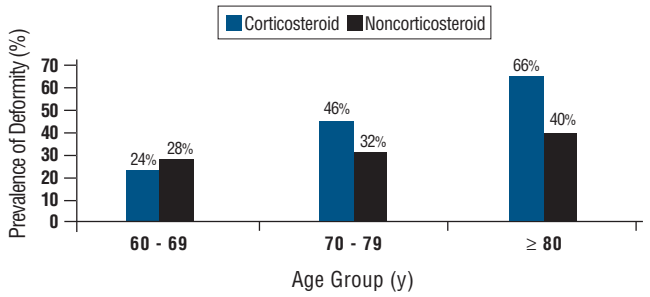
Since corticosteroid therapy does not provide maintenance benefits for either UC or CD, all attempts should be made to taper corticosteroids after induction of clinical remission to minimize long-term sequelae, including the impact of corticosteroids on bone.[36]

Monitoring, Prevention, and Treatment of Osteoporosis in Patients With IBD

Advances in BMD measurement techniques and an improved understanding of risk factors for osteoporosis have made it possible to identify patients at high risk of fracture. It has been estimated that, for each standard-deviation decrease in femoral neck bone density, there is a 2.6-fold increase in the age-adjusted risk of hip fracture.[46] Bone density screening by dual-energy x-ray absorptiometry (DEXA) carries the advantages of reproducibility of results, rapidity (15 minutes), low radiation exposure, and low cost. However, it is important to note that DEXA cannot differentiate osteopenia from osteomalacia, so 25-hydroxy vitamin D levels should be obtained for all patients to document adequate vitamin D status in patients with small bowel disease, small bowel resections, or poor intake of vitamin D.[50] The optimal timing of bone densitometry and the subset of patients who should be screened have not yet been established in IBD. Although it seems prudent to screen all patients early, when intervention would have the greatest impact, this may not be the most cost-effective strategy. Therefore, one could consider limiting screening to certain high-risk groups, including postmenopausal women, children, and elderly patients. Although increasing age is a well-known general risk factor for osteoporosis, it must be borne in mind that bone health is particularly important in children and adolescents, who have not yet attained peak bone mass and whose growth may be hampered by IBD.[53]

Institution of preventive therapy is an important aim. Routine measures to reduce the risk of osteoporosis should be initiated in all patients. These include lifestyle modifications, as well as supplemental calcium and vitamin D. A discussion of therapeutic options may be found in the National Osteoporosis Foundation's *Physician's Guide to Prevention and Treatment of Osteoporosis*.[51] Several different antiresorptive drugs are currently approved for the prevention and/or treatment of osteoporosis, including HRT, raloxifene, calcitonin, and two bisphosphonates—alendronate and risedronate. Postmenopausal women should be counseled to consider HRT in order to gain its benefits on bone as well as on other organ systems unless certain contraindications (eg, breast cancer) are present. Its efficacy in prevention of bone loss has been established in postmenopausal women with IBD.[58] Whereas all of the drugs noted have been shown to lower the risk of vertebral fracture, only the bisphosphonates are known to lower the risk of hip fractures and have been studied in IBD-related osteoporosis. Bisphosphonates inhibit bone resorption by direct inhibition of the action of osteoclasts. They have a sustained effect because of their long half-life in bone.[53] Among the available agents, alendronate has been shown to be effective in the treatment of glucocorticoid-induced osteoporosis.[59] Risedronate, in addition to being safe and effective for the treatment of corticosteroid-induced osteoporosis, also has been shown to prevent glucocorticoid-induced bone loss.[60,61] Parathyroid hormone, in combination with estrogen, has also been shown to stimulate bone formation by increasing osteoblast production.[62]

FIGURE 2
INCREASE IN THE PREVALENCE OF VERTEBRAL DEFORMITY WITH AGE AND CORTICOSTEROID USE



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The prevention and treatment of osteoporosis in patients with UC and CD requires a proactive approach. It is important that all physicians who treat IBD recognize that their patients—particularly those receiving corticosteroid therapy—are at increased risk for osteoporosis and associated fractures. Prophylactic measures are recommended for all patients when they initiate corticosteroid treatment. Osteoporotic fracture is a devastating event that, with careful identification and treatment of patients at increased risk, can be avoided.

CONCLUSION

The many complications associated with IBD can confer a significant burden of suffering on patients. Fortunately, a number of these complications are treatable, and some are preventable. Many of the most common extraintestinal manifestations follow the course of IBD and improve following successful medical or surgical treatment of IBD. Although the specter of CRC is raised for patients with IBD, certain medications, including the 5-ASAs, may decrease CRC risk. Dysplasia surveillance with endoscopies, while an imperfect tool, can provide a potential means of identifying precancerous lesions or cancers at an early, curable stage. Finally, although all patients with IBD, and especially those receiving corticosteroid therapy, are at an increased risk for osteoporosis, there are pharmacologic options for its prevention and treatment. Special care must be considered for female patients with IBD as they approach menopause. In these patients, the risks of osteoporosis are compounded. A heightened awareness of the scope of these problems and how they are managed will do much to ensure optimal patient care.

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EXTRAINTESTINAL MANIFESTATIONS AND LONG-TERM COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE

3rd in a Series of 3 Newsletters

ANSWER SHEET, PROGRAM EVALUATION, AND CME CREDIT REQUEST

Posttest

Instructions: To receive CME credit, kindly complete the posttest and evaluation.
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Release date: August 2002 Expiration date: August 2004

A score of at least 70% is required to receive CME credit.

1. Which of the following statements is true regarding extraintestinal manifestations associated with inflammatory bowel disease (IBD)?
   a. The most common extraintestinal manifestations occur in the skin, eyes, joints, and biliary tract.
   b. Immune dysregulation is believed to underlie both IBD and many of the common extraintestinal manifestations.
   c. Many of the common extraintestinal manifestations follow a course independent of IBD and thus require specific treatments in addition to those used to control bowel disease.
   d. a and b
   e. All of the above
2. Which of the following extraintestinal manifestations occur more frequently in women than in men?
   a. Erythema nodosum and uveitis/iritis b. Pyoderma gangrenosum and ankylosing spondylitis
   c. Primary sclerosing cholangitis d. Erythema nodosum and pyoderma gangrenosum
3. Among the most common extraintestinal manifestations, which is potentially the most serious because of lack of effective therapy?
   a. Erythema nodosum b. Colitic arthritis
   c. Primary sclerosing cholangitis d. Pyoderma gangrenosum
4. Which of the following is associated with increased colorectal cancer (CRC) risk in patients with ulcerative colitis (UC)?
   a. Increasing duration of disease b. Increasing age
   c. Greater disease extent d. All of the above
   e. None of the above
5. Which of the following drugs has been associated with a lower risk of CRC in UC?
   a. Azathioprine and 6-mercaptopurine b. Mesalamine
   c. Methotrexate d. Corticosteroids
6. Which of the following actions is recommended following endoscopy for dyplasia surveillance in patients with UC?
   a. A finding of definite dysplasia, regardless of grade, is an indication for colectomy.
   b. If the initial endoscopy findings are negative, a repeat endoscopy should be performed within 2 months.
   c. After 8 years of disease, the patient should be counseled to consider prophylactic colectomy.
   d. If the initial endoscopy findings are negative, a repeat endoscopy should be performed annually.
7. Osteoporosis associated with IBD occurs in:
   a. More than half of women over 54 years of age
   b. Approximately 60% of patients receiving long-term corticosteroid therapy
   c. Only pediatric patients with Crohn's disease
   d. Approximately 20% to 30% of patients with IBD
8. Please choose the risk factor for osteoporosis that is specific to patients with IBD.
   a. Inflammatory cytokines b. Female gender
   c. Personal history of fracture as an adult d. Increasing age
9. Effects of glucocorticoids on bone include:
   a. Decreased osteoclast-mediated bone resorption and increased osteoblast-mediated bone formation
   b. Increased intestinal absorption of calcium and phosphate
   c. Reduction in circulating levels of sex hormones
   d. Increased attachment of osteoblasts to bone matrix
10. Which of the following agents has been shown to prevent glucocorticoid-induced osteoporosis?
    a. Thiazide diuretics b. Calcium and vitamin D
    c. Methotrexate d. Risedronate
    e. All of the above

Please record your posttest answers: 1. ____2. ____3. ____4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

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We hope this newsletter has provided information that will be useful in your practice. Your evaluation will help us plan future programs. May we have your comments?

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This program is supported by an unrestricted educational grant from Procter & Gamble Pharmaceuticals, Inc.